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Signed A M Brewer

Dated 30 August 2001

For official use

THE PATENT OFFICE
M
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Your reference
PCS10946WMD-PROV

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Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

NEW PROCESS

20 DEC 2000

0031094.6

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

UK postcode CT13 9NJ
(if applicable)

1271001

Country UNITED KINGDOM

ADP number
(if known)

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

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UK postcode
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Country

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(if known)

3
An address for service in the United Kingdom must be supplied.
Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇
Please give details below

Agent's name
DR. W.M. DADSON
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone number*(if available)*

ADP number
(if known)

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10946WMD-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

⬇ ***please give details below***

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	5 ✓	Description	8 ✓
Abstract	1 ✓	Drawing(s)	W

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

9 Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed W. M. [signature] Date 20/12/2000 *(day month year)*

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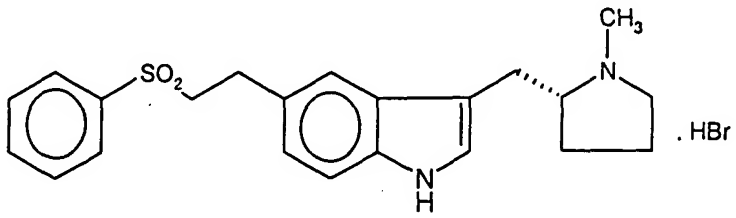
NEW PROCESS

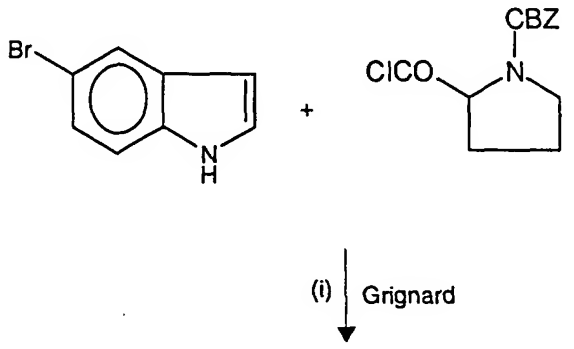
The present invention is concerned with an improved process for the preparation of the anti-migraine drug, (R)-5-(2-benzenesulphonylethyl)-3-N-methylpyrrolidin-2-ylmethyl)-1H-indole (eletriptan), available commercially as the hydrobromide salt:

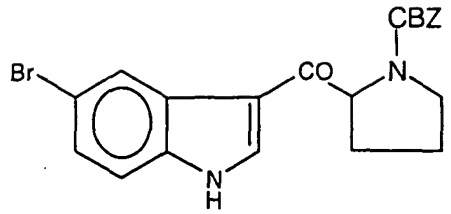


and with an intermediate and dimer-free products obtained thereby.

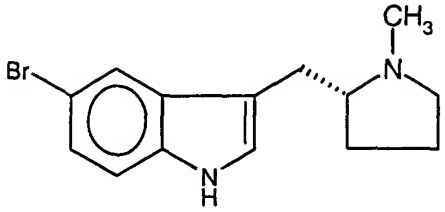
European Patent No. 0592438 describes the preparation of eletriptan by the catalytic reduction of (R)-5-(2-benzenesulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, which compound is prepared by (i) reacting N-benzyloxycarbonyl-D-proline acid chloride with 5-bromoindole in the presence of a Grignard reagent, (ii) reducing the resulting (R)-3-(N-benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-bromo-1H-indole to give (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole and (iii) reacting same with phenyl vinyl sulphone in the presence of a palladium catalyst, a triarylphosphine and a base.

The complete sequence may be represented as follows:

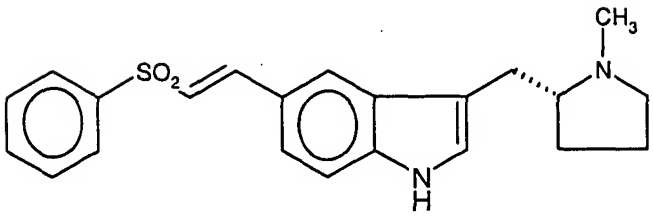




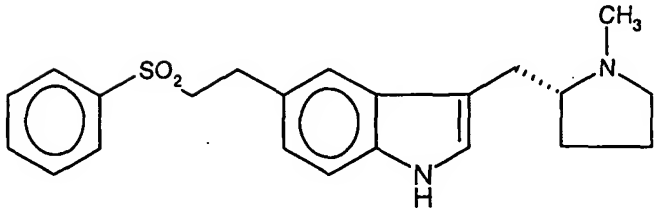
(ii) Reduction



(iii) $PhSO_2CH=CH_2$

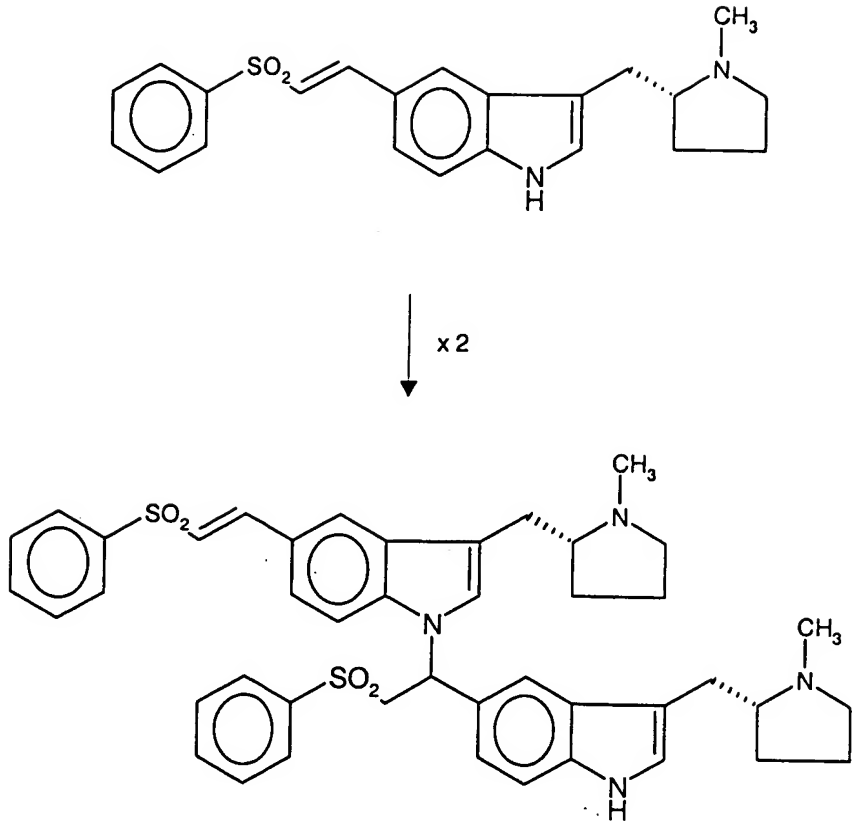


Catalytic reduction



(I)

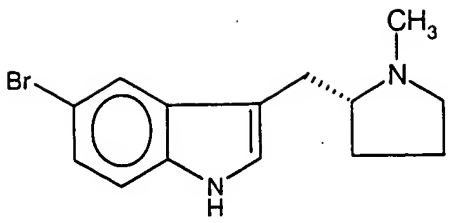
While the foregoing sequence produces eletriptan of formula (I) in reasonable yield, it has been found that the (R)-5-(2-benzenesulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole precursor is prone to dimerise when attempting to recrystallise in impure form and/or drying prior to catalytic reduction:



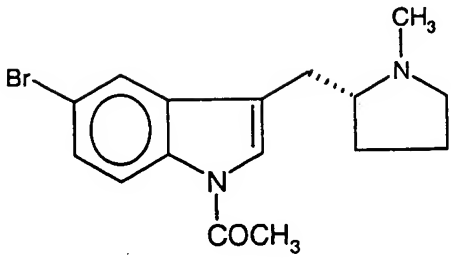
Not only does the formation of this dimeric impurity reduce the yield of eletriptan, but, perhaps more importantly, it requires the costly and time-consuming removal of said dimer in order to provide hydrobromide salt of sufficient purity to meet the stringent standards required for regulatory approval.

As a result of this difficulty, we have now developed an alternative route to eletriptan which avoids the use of a precursor which is prone to dimerisation. Specifically, the process of the invention comprises the preparation of eletriptan by the hydrolysis of (R)-1-acetyl-5-(2-benzenesulphonylethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, which compound may conveniently be prepared by (i) N-acetylating (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, (ii) reacting the resulting (R)-1-acetyl-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole with phenyl vinyl sulphone in the presence of a palladium catalyst, a triarylphosphine and a base to give (R)-1-acetyl-5-(2-benzenesulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole and (iii) catalytically reducing same.

The complete sequence may be represented as follows:

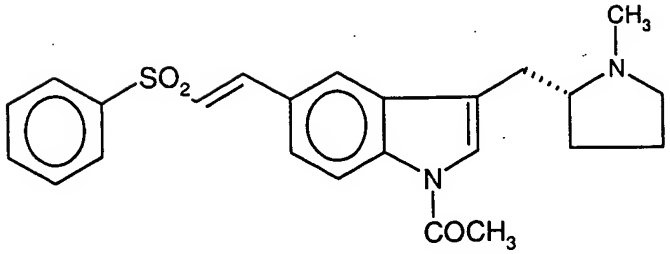


(i) N-acetylation



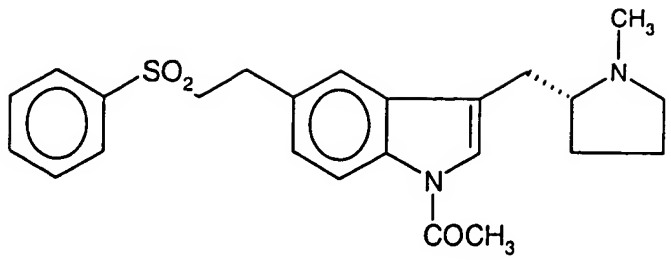
(IV)

(ii) $PhSO_2CH=CH_2$



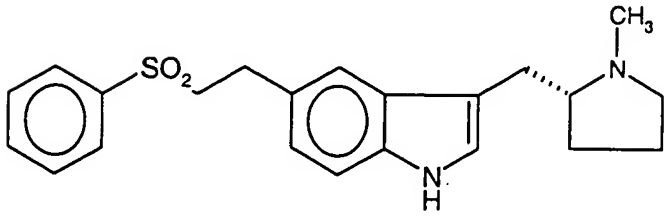
(III)

(iii) Catalytic reduction



(II)

Hydrolysis



(I)

By the use of this process, it is possible to avoid the formation of unwanted dimer and thereby obtain eletriptan of high purity in good yield without the subsequent costly and time-consuming purification steps needed to remove the dimeric impurity.

Thus according to the present invention, there is provided a process for the preparation of a compound of formula (I) which comprises hydrolysis of a compound of formula (II), typically under basic conditions, more especially potassium carbonate in methanol/water.

According to another aspect of the invention, the compound of formula (II) used in the process may be obtained by catalytic reduction of a compound of formula (III), typically using hydrogen or a hydrogen source in the presence of a suitable catalyst. The reduction is typically carried out using hydrogen at a pressure of from 1 to 15 atmospheres or using a hydrogen source such as ammonium formate or formic acid. Suitable catalysts include palladium on carbon, for example, 5% w/w Pd/C, Raney nickel, platinum oxide, rhodium, or ruthenium. The reduction is conveniently carried out in the presence of an acid, for example, methanesulphonic acid, acetic acid, or trifluoroacetic acid. The compound of formula (II) so obtained is conveniently slurried with cold aqueous tetrahydrofuran before hydrolysis to the compound of formula (I).

The invention specifically provides the aforementioned compound of formula (II) which has not hitherto been described.

According to yet another aspect of the invention, the compound of formula (III) used in the process may be obtained by treating a compound of formula (IV) with phenyl vinyl sulphone in the presence of a palladium catalyst, a triarylphosphine and a base in accordance with the process described in Example 57 of US Patent 5,607,951.

According to yet a further aspect of the invention, the compound of formula (IV) used in the process may be obtained by the N-acetylation of (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, also in accordance with the process described in Example 57 of aforementioned US Patent No. 5,607,951.

Eletriptan obtained by the process of the invention may be converted to a pharmaceutically acceptable acid addition salt by treatment with an appropriate acid; said conversion may conveniently be carried out *in situ* without isolation of the compound of formula (I). A particularly preferred salt is the hydrobromide obtained by treatment with hydrobromic acid.

Thus according to the present invention, there is also provided dimer-free eletriptan and pharmaceutically acceptable salts thereof, particularly the hydrobromide, and pharmaceutical compositions comprising same.

The process of the invention may be illustrated by the following Example of the preparation of (R)-5-(2-benzenesulphonylethyl)-3-N-methylpyrrolidin-2-ylmethyl)-1H-indole (I) and its hydrobromide salt:

EXAMPLE

(a) Preparation of (R)-1-acetyl-5-(2-benzenesulphonylethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole (II)

To a solution of the compound of formula (III) (200g) prepared by the method

described in Example 57 of aforementioned US Patent No. 5,607,951 in acetone (2.0L) was added water (0.5L). Methanesulphonic acid (43.2g, 0.95 equiv.) was added dropwise and the resulting solution stirred for 5 minutes before adding 5% w/w Pd/C catalyst (89.0g, Johnson Mattey Type 58, 50% wet). The solution was hydrogenated at room temperature at 200psi hydrogen for 18 hours.

The catalyst was removed by filtration and the filtrate stripped to give an acetone-free slurry. To this was added dropwise 40% aqu. NaOH (30mL) followed by water (1.5L). The resulting slurry was stirred for 20 minutes and further 40% aqu. NaOH (20mL) added. After granulation for 2 hours under vigorous stirring, the suspension was filtered and sucked dry for 30 minutes to give a beige damp solid which was either

(i) dried at 45°C to give the desired product (193.0g, yield 95%) or

(ii) taken up in tetrahydrofuran (1.6L) to which was added water (1.5L in total) over 10 minutes. The resulting suspension was stirred vigorously for 18 hours, filtered and sucked dry for 30 minutes to give the desired product as a beige damp solid (corrected weight 129.0g, yield 67%).

Either form may be used directly in step (b):

(b) <u>Preparation of (R)-5-(2-benzenesulphonylethyl)-3-N-methylpyrrolidin-2-ylmethyl)-1H-indole (I)</u>

To a solution of the compound of formula (II) (95.9g) from step (a)(i) or (ii) in acetone (1L) and methanol (0.1L) was added K_2CO_3 (46.8g, 1.5 equiv.) and the resulting mixture stirred for 24 hours. To this was added charcoal (50g) followed an hour later by anhy. $MgSO_4$ (300g). The resulting suspension was stirred for 1 hour and filtered. The filtrate was stripped to give a damp solid which was dried *in vacuo* at 45°C to give the desired product (79.3g, 91.8%).

In the case where the compound of formula (I) is to be converted to a pharmaceutically acceptable acid addition salt, isolation of the compound of formula (I) may be avoided by directly treating the solution obtained by hydrolysis with the appropriate acid, for example, hydrobromic acid to give the hydrobromide salt:

(c) Preparation of (R)-5-(2-benzenesulphonylethyl)-3-N-methylpyrrolidin-2-ylmethyl)-1H-indole (I) and *in situ* hydrobromination thereof

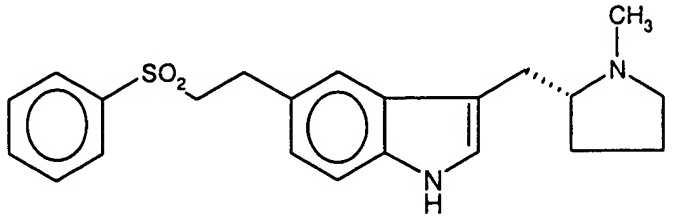
To a solution of the compound of formula (II) (95.9g) from step (a)(i) or (ii) in acetone (1L) and methanol (0.1L) was added K_2CO_3 (46.8g, 1.5 equiv.) and the resulting mixture stirred for 24 hours. To this was added charcoal (50g) followed an hour later by anhy. $MgSO_4$ (300g). The resulting suspension was stirred for 1 hour and filtered.

The filtrate was partially concentrated by azeotropic distillation to remove methanol and the volume readjusted to 0.45L with acetone. A solution of 48% w/v HBr (33.2g, 0.95 equiv.) in acetone (50mL) was added dropwise and the resulting suspension stirred for 72 hours. This was filtered, sucked dry for 30 minutes and dried *in vacuo* at 45°C to give the desired product as slightly beige crystals (71.8g, 68.5%).

In a preferred embodiment of the invention, certain steps may be 'telescoped' in order to reduce handling and accelerate processing time. For example, as indicated in step (a)(ii), drying the compound of formula (II) prior to hydrolysis may be avoided by using damp material slurried in aqueous tetrahydrofuran. Likewise, as indicated in step (c), isolation of the compound of formula (I) before conversion to a salt may be avoided by forming the salt *in situ*.

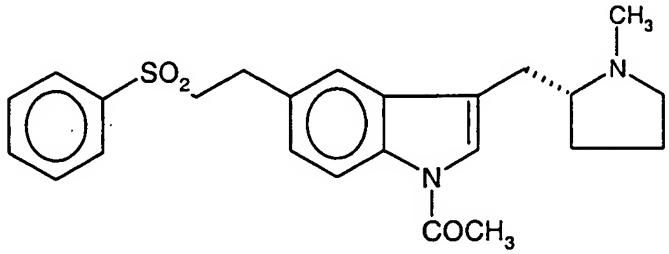
CLAIMS

1. A process for the preparation of a compound of formula (I)



(I)

which comprises hydrolysis of a compound of formula (II)

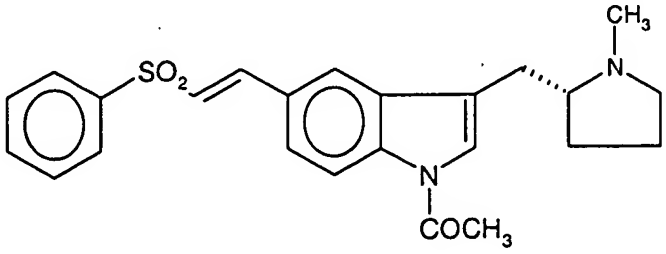


(II)

2. A process according to Claim 1 which is carried out under basic conditions.

3. A process according to Claim 2 wherein said hydrolysis is performed using potassium carbonate in methanol/water.

4. A process according to any of Claims 1 to 3 wherein the compound of formula (II) is obtained by catalytic reduction of a compound of formula (III)



(III)

5. A process according to Claim 4 wherein said reduction is carried out using hydrogen or a hydrogen source in the presence of a suitable catalyst.

6. A process according to Claim 5 wherein said reduction is carried out using hydrogen at a pressure of from 1 to 15 atmospheres.

7. A process according to Claim 5 wherein said reduction is carried out using a hydrogen source which is ammonium formate or formic acid.

8. A process according to according to any of Claims 4 to 7 wherein said catalyst is palladium on carbon, Raney nickel, platinum oxide, rhodium, or ruthenium.

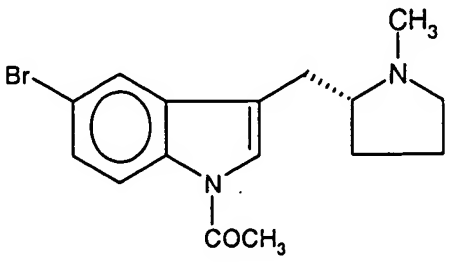
9. A process according to Claim 8 wherein said catalyst is 5% w/w palladium on carbon.

10. A process according to any of Claims 4 to 9 wherein the catalytic reduction is carried out in the presence of an acid.

11. A process according to Claim 10 wherein said acid is methanesulphonic acid, acetic acid, or trifluoroacetic acid.

12. A process according to any of Claims 4 to 11 wherein the compound of formula (II) obtained by catalytic reduction is slurried with cold aqueous tetrahydrofuran before hydrolysis to the compound of formula (I).

13. A process according to any of Claims 4 to 12 wherein the compound of formula (III) is obtained by treating a compound of formula (IV)



(IV)

with phenyl vinyl sulphone in the presence of a palladium catalyst, a triarylphosphine and a base.

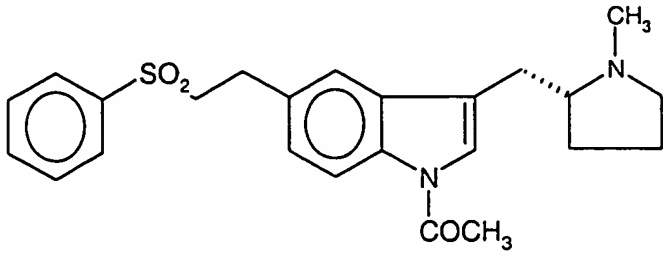
14. A process according to Claim 13 wherein the compound of formula (IV) is obtained by N-acetylating (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

15. A process according to any of Claims 1 to 14 wherein the compound of formula (I) so obtained is converted to a pharmaceutically acceptable acid addition salt by treatment with an appropriate acid.

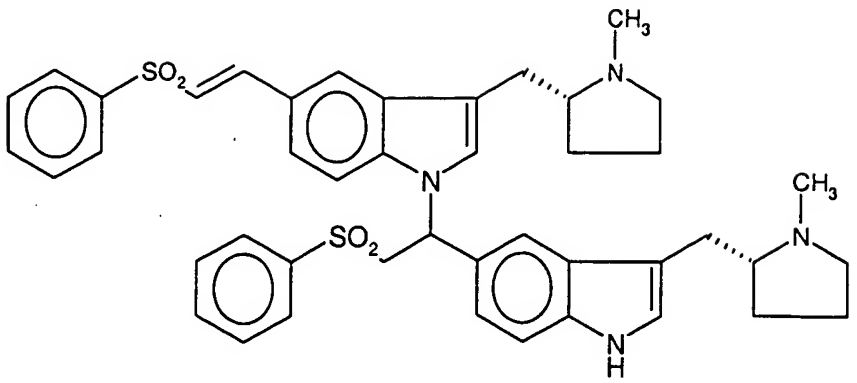
16. A process according to Claim 15 wherein said conversion is carried out *in situ* without isolation of the compound of formula (I).

17. A process according to Claim 15 or 16 wherein the acid is hydrobromic acid and the resulting salt is the hydrobromide.

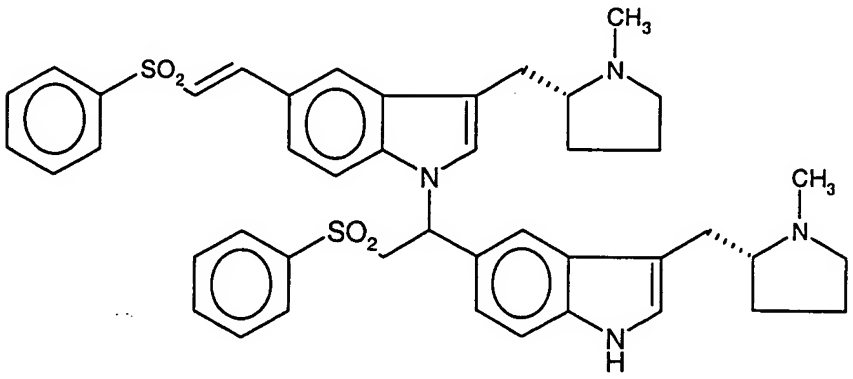
18. The compound of formula (II):



19. Eletriptan which is substantially free of

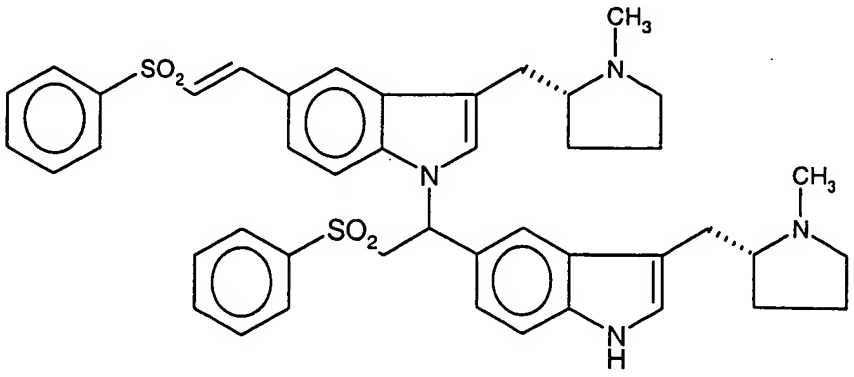


20. A pharmaceutically acceptable acid addition salt of eletriptan which is substantially free of



21. A pharmaceutically acceptable acid addition salt of eletriptan according to Claim 20 which is the hydrobromide.

22. A pharmaceutical composition comprising eletriptan or a pharmaceutically acceptable acid addition salt thereof which is substantially free of



and a suitable carrier or excipient.

23. A composition according to Claim 22 wherein said pharmaceutically acceptable acid addition salt is the hydrobromide.

ABSTRACT

NEW PROCESS

The present invention is concerned with an improved process for the preparation of the anti-migraine drug, (R)-5-(2-benzenesulphonylethyl)-3-N-methylpyrrolidin-2-ylmethyl)-1H-indole (eletriptan), available commercially as the hydrobromide salt, and with an intermediate and dimer-free products obtained thereby.